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(54) **Contraceptive compositions based on esters of levo-norgestrel.**

(57) A small group of esters of levo-norgestrel have been found to be unexpectedly effective as long term contraceptive agents. The esters are:

levo-norgestrel butanoate,
levo-norgestrel cyclopropylcarboxylate
levo-norgestrel cyclobutylcarboxylate
levo-norgestrel cyclopentylcarboxylate 3-oxime, or
levo-norgestrel cyclohexylcarboxylate 3-oxime

The esters may be formulated in a pharmaceutically acceptable aqueous medium, preferably in the form of a microcrystalline suspension of particle size in the range 3 to 10 μ expressed as the 50% cumulative oversize in the Coulter distribution curve. A suitable human dosage 15 contains from 1 to 50 mgms of the ester.

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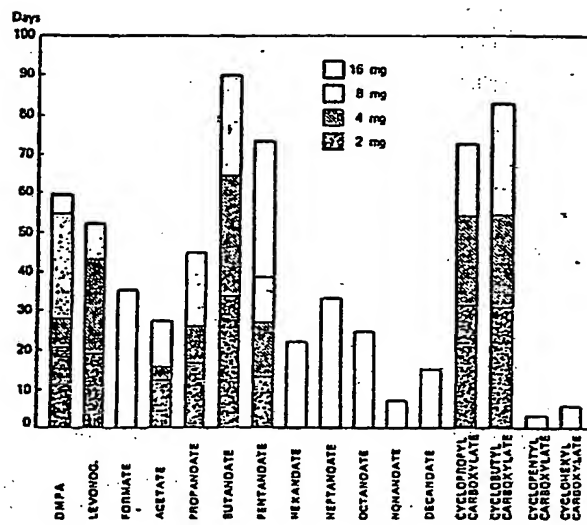


Figure 1. Duration of total estrus suppression following a single subcutaneous injection of levonorgestrel or its esters to rats.

CONTRACEPTIVE COMPOSITIONS BASED ON ESTERS OF
LEVO-NORGESTREL

This invention relates to injectable therapeutic compositions based on certain esters of levo-norgestrel which have valuable long-acting contraceptive properties.

The pharmacological effects of steroids such as levo-norgestrel, progesterone, nortestosterone and norethisterone have been known for very many years.

10 However, their effects as contraceptive agents are relatively short lasting with the consequence that injections at frequent intervals would be required to maintain fertility control.

Attempts have been made to extend the effective
15 term of contraceptive activity by esterifying the steroids, a very desirable term being three months or more. However, to date, only two injectable contraceptive preparations have been made available. These are depot-medoxy-progesterone acetate (DMPA), which initially has to be injected at 2-monthly

intervals, and norethisterone enanthate. Both of these suffer from several disadvantages one of them being that although they were developed in the 1960s they have still not been approved by the US Food and Drug Administration.

5 There is a great need, particularly in developing countries, for an injectable contraceptive which is safe and is effective for a longer period.

 With this in mind, over 200 new derivatives of synthetic steroids known to be efficient and "safe" as contra-
10 ceptive agents have been selected and synthesised. The derivatives were 17-esters of acids of varying chain lengths, nature and degree of unsaturation, (double and/or triple bonds, dienes, enynes, allenes), ring size (cyclopropane to cyclohexane, with or without substitution). Acids
15 containing benzene and furan rings as well as some unusual naturally occurring acids were employed. Oximes of several of the esters and few ethers containing alkyl, aryl and silyl substituents were also prepared.

 These were subjected to a biological screening
20 programme designed to uncover new and effective sustained-release injectable contraceptives, the compounds being tested as injectable oily solutions or aqueous suspensions. The initial test was to determine the duration of suppression of estrus in female rats, with DMPA and norethisterone
25 enanthate being used as comparison standards. The most

promising compounds were then tested in primates.

In general, the tests indicated a lack of correlation between structure and activity, but it was found that of all the compounds screened in the programme
5 five showed outstanding properties when injected as a micro crystalline suspension in an aqueous medium. The five compounds were levo-norgestrel butanoate, cyclopropylcarboxylate, cyclobutylcarboxylate, cyclopentylcarboxylate 3-oxime and cyclohexylcarboxylate
10 3-oxime.

It was noted that the duration of action of these five longer acting compounds was also dependent on the nature of the pharmaceutical composition into which they were formulated, even better results being
15 achieved when the compounds were injected as an aqueous suspension of crystals of a particular particle size range. Further, the longer term effectiveness was achieved even with doses smaller than the normal doses of DMPA.

20 The present invention therefore provides an ester of levo-norgestrel and an aliphatic acid characterized in that the ester is:

levo-norgestrel butanoate
levo-norgestrel cyclopropylcarboxylate
levo-norgestrel cyclobutylcarboxylate
levo-norgestrel cyclopentylcarboxylate 3-oxime
5 levo-norgestrel cyclohexylcarboxylate 3-oxime

The present invention also provides injectable
contraceptive compositions which are suspensions
in a pharmaceutically acceptable aqueous medium of
one of these selected esters, preferably of micro-
10 crystals of particle size in the range 3 to 10μ
expressed as the 50% cumulative oversize in the Coulter
distribution curve.

Preferably, the composition is in a unit
dosage form containing 1 to 50 mgms of the levo-norgestrel
15 ester.

In general, it is desirable that any
administration of steroids is in the smallest dose
effective for the purpose and it is a feature of this
invention that the compositions if injected at intervals
20 appropriate for DMPA can contain a smaller amount of the
steroid, and further, that the dose may still be smaller

even when the injections are at longer intervals of say,
3 months.

For example, the long-acting contraceptive
properties of levo-norgestrel 17 β -cyclobutylcarboxylate
5 in aqueous microcrystalline suspension extended beyond
a period of 91 days, at a dose of 16 mg in the rat, while
(a microcrystalline suspension of DMPA has an average
suppression duration of 63.7 days (59.6 - 71.2) and
an oily solution of norethisterone enanthate an average
10 duration of 23.1 days (13.5 - 34.8). More importantly,
the cyclobutylcarboxylate at a dose of 8 mg in the rat
gives the same inhibition as DMPA at 16 mg. Data
provided on the pharmacokinetics of levo-norgestrel
cyclobutylcarboxylate in the monkey *Macaca mulata* showed
(15 that measurable levels of levo norgestrel are still
present in the circulation longer than 100 days after
injection.

The invention also provides therefore, a
method of contraception wherein there is injected into
20 a human female a dose of an above-mentioned composition

containing microcrystals of one of the above selected levo-norgestrel esters of particle size in the range 3 to 10μ , the dose containing from 1 to 50 mgms of the ester.

Preferably, the method of contraception is a continuous one, the injections being given at intervals of from two to six months, though injections can be given at one month intervals if necessary. A suitable dose at one month intervals is from 1 to 6mgms, and at six month intervals is from 20 to 50 mgms.

10 By levo-norgestrel is meant D-(-)-13 β -ethyl-17 α -ethynyl-17 β -hydroxygon-4-en-3-one.

The esters used in this invention are prepared by conventional methods as illustrated by the following:

15 In a preparation of levo-norgestrel cyclobutyl-carboxylate thallous ethoxide (0.036 mol) was added to a solution of levo-norgestrel (0.03 mol) in 100 ml of dry benzene. The benzene was distilled off slowly but the volume of the reaction mixture was maintained at about 100 20ml by the dropwise addition of dry benzene thereto. After 200 ml of the benzene were distilled off, the reaction mixture was cooled in an ice water bath. Thereafter 0.039 mol of cyclobutane carboxylic acid, in its acyl chloride

- 7 -

form, was added dropwise to the reaction mixture which was then refluxed for 5 hours. After cooling, the reaction mixture filtered through a bed of kieselguhr and the resulting precipitate was washed five times with 20 ml of benzene. The solvent was then evaporated and the resulting residue was purified in accordance with conventional procedures.

Although this process gives a useful yield it is difficult to avoid traces of thallium in the final esters.

10 In an alternative process, trifluoroacetic anhydride (13 ml = 19.33g, 92.03 ml = mM) and cyclobutane carboxylic acid (8.0 ml = 8.37g, 83.60 mM, freshly distilled) were dissolved in benzene (240 ml) and stirred under anhydrous conditions for 30 minutes. Levo-norgestrel 15 (15g, 48.00mM) was then added and the solution was stirred at room temperature for 40 minutes. The reaction mixture was then diluted with ice water and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution (2X), water (2X) and brine (1X), dried (Na₂SO₄) 20 filtered, and concentrated in vacuo. The residue was then dissolved in acetone and an equal volume of hexane was added to it. Crystallization took place when it was set aside, yielding 10.5g of the above-identified ester having a melting point of 229 - 232°C.

25 In a further alternative process the steroid

may be esterified by reaction with the acid chloride in the presence of excess acid and a small amount of pyridine, or by using 4-dimethylamino pyridine as a coupling agent.

The corresponding cyclopropyl carboxylate
5 (M.Pt. 211-4°C) and butyrate ester (M.Pt. 214-9°C) are made by analogous methods.

The oximes are prepared by reacting the appropriate ester with hydroxylamine hydrochloride.

For example, levo-norgestrel cyclopentylcarboxylate
10 3-oxime was prepared as follows:

Levo-norgestrel 17 β -cyclopentyl carboxylate (588 mg) was dissolved in pyridine (6 ml) and hydroxylamine-hydrochloride (550 mg) added and the mixture heated at 100°C for 7 minutes and cooled in an ice-bath. Hydrochloric acid (1N, 45 ml) was added dropwise and the mixture
15 extracted with ethyl acetate. The ethyl acetate extract was washed with 1N HCl, water, saturated sodium bicarbonate solution, water and brine and dried over sodium sulphate. Evaporation of the solvent and crystallization of the
20 residue from ethanol-water and drying in vacuo gave the oxime (593 mg), mp 172.5-174°C; HPLC (μ Porasil, heptane: isopropanol 96:4, 2 ml/min, U.V. 254 nm, anti isomer:syn isomer 53:47).

A similar preparation of levo-norgestrel 17 β -cyclo-
25 hexyl carboxylate 3-oxime gave the oxime (2.2 g) mp

167-169°C as a mixture of the anti and syn isomers (53:47 by HPLC - Porasil column, heptane: isopropanol 96:4.

The microcrystalline suspensions of the steroid esters were made by milling the appropriate amount of the ester in an aqueous medium consisting of:

	Benzyl alcohol	1.000% w/v
	Sodium carboxymethyl cellulose	0.500% w/v
	Disodium hydrogen phosphate dihydrate	0.376% w/v
10	Sodium dihydrogen phosphate dihydrate	1.495% w/v
	Polysorbate 80	0.200% w/v
	Water for injection to	100.000%

The milling was carried out in a Glen Creston M270 micronising ball mill equipped with an agate container and ball. A milling period of up to an hour was required to reduce the particles of ester to the required size.

The bioassay used to determine the duration of action of the contraceptive compositions involved measuring the suppression of estrus in female rats. The compositions were used at four dosage levels, i.e. 2, 4, 8 and 16 mg/rat.

Figure 1 of the accompanying drawings, shows the effect of various dosages of the compositions based on three of the selected esters together with the effect of

similar compositions based on esters closely related to those used in the three compositions of this invention.

It will be noted that the three compositions based on the butanoate, cyclopropyl carboxylate and cyclo-
5 butyl carboxylate esters suppress estrus to a highly unexpected degree and even at a dosage of 8 mg/rat give better suppression than DMPA at a dosage of 16 mg/rat.

Figure II of the accompanying drawings illustrates the effect of the cyclobutyl carboxylate ester
10 when formulated in different types of compositions. In Figure II the percentage of rats which returned to estrus (tested in groups of ten) is plotted against weeks and the symbols used are as follows:

- 15 0 - aqueous microcrystalline suspension
 of ester of particle size 3 to 10 μ as
 hereinbefore defined
- \triangle - solution in sesame oil
- ∇ - solution in ethyl oleate

The plots illustrate the longer term effect
20 of the ester when micro-dispersed in aqueous medium.

Similar results are obtained using the other two esters used in this invention.

A more wide-ranging comparison of the butanoate, cyclopropylcarboxylate and cyclobutylcarboxylate esters with other esters of levo-norgestrel is given in the following Table I. Depending on the physical nature of the ester, formulation was either as a microcrystalline suspension in an aqueous vehicle or as a solution in ethyl oleate. The composition of the aqueous vehicle was as given above.

The long-acting properties of each formulation were determined in estrus suppression assay employing virgin, mature (180-200 g) cycling rats of the Sprague-Dawley strain purchased from Charles River Laboratories, USA. Upon receipt the animals were smeared daily for cyclicity and only those animals showing two consecutive normal cycles were used.

Each animal was injected subcutaneously with 0.8 ml of the test preparation on the same day regardless of the stage of the cycle. Each compound was initially tested on ten rats. A series of initial tests with injections of 16 mg/animal were followed by studies at dose levels of 8, 4 and 2 mg/animal where necessary. An aqueous microcrystalline suspension of medroxyprogesterone acetate was used as standard. Daily smears were taken starting on the day after injection and continued until such time that cornification of vaginal epithelium was observed and cycling was re-established.

Duration of cornification suppression is expressed as the

total number of days minus two. The appearance of cornification was not always followed by the return of normal estrus cycles. The majority of experiments were terminated at 91 days post injection even though some of the animals
5 had not exhibited cornified smears.

Numerous estrus suppression assays with an aqueous microcrystalline suspension of medroxyprogesterone acetate at different doses have produced the following durations of suppression: at 2 mg/rat - 20.9 days, at 4 mg/rat - 28.2
10 days, at 8 mg/rat - 55.5 days, and at 16 mg/rat - 60.0 days. At the most commonly employed dose, 8 mg/rat, the duration of activity of the standard varied from 35.1 ± 2.0 to 73.2 ± 3.4 . At 16 mg/rat the suppression of estrus was much more uniform ranging from 59.6 ± 2.4 days to 71.2 ± 9.0 .

15 Data obtained in seven different experiments utilizing the cyclobutylcarboxylic ester of levo-norgestrel indicate a more linear duration of suppression of estrus. At 2 mg/rat, estrus suppression was obtained for 31.9 days, at 4 mg/rat it was 55.7 days and at 8 mg/rat it was 89.2 days.
20 The duration of suppression at 8 mg/rat was unrealistically low due to the arbitrary termination of majority of the experiments at 91 days post injection. In two separate experiments which were continued until all animals exhibited a cornified smear, the average durations of suppression were
25 103.3 ± 9.3 and 124.3 ± 9.2 days. With the cyclopropyl-

carboxylate the equivalent data is as follows: at 4 mg/rat

- 55.6 days and at 8 mg/rat, - 74.0 days. With the butanoate it was at 2 mg/rat, - 34.4 days, at 4 mg/rat, - 65.1 days and at 8 mg/rat, <91 days.

- 5 In the series shown in Table 1 and Fig.1, several interesting structure activity relationships can be observed. Among the straight chain fatty acid esters prepared as microcrystalline suspensions, activity increased sharply from formate to butanoate and then declined just as rapidly.
- 10 Introduction of a methyl group at C2 of propanoate, at C3 of butanoate and at C4 of pentanoate resulted in marked decreases in activity. Among the cyclic esters, cyclopropylcarboxylate and cyclobutylcarboxylate were long-acting whereas cyclopentylcarboxylate and cyclohexylcarboxylate
- 15 were short acting.

- In the series, the influence of formulation on the duration of action was very pronounced with some of the esters and lacking with others. This is illustrated in Table 11. The cyclobutylcarboxylic ester prepared as a
- 20 microcrystalline suspension in ethyl oleate had only approximately 40% of the activity of the aqueous suspension. Further reduction in activity was observed when this compound was prepared as a solution in a 50:50 mixture of ethyl oleate and benzyl benzoate (BB). Similar differences in activity

were observed among formulations having different particle size distributions; microcrystalline suspensions being more active than the coarser preparations.

A similar series of tests using formulations based
5 on levo-norgestrel ester oximes also produced unexpected results as illustrated in Fig. 111.

Most were tested as aqueous microcrystalline suspensions of the oxime though in the cases of the oximes of levo-norgestrel butanoate, levo-norgestrel isobutanoate,
10 levo-norgestrel cyclopropylcarboxylate and levo-norgestrel itself, the ester oxime could not be formulated as an aqueous microcrystalline suspension and had to be formulated as a solution in ethyl oleate.

Although the cyclopentylcarboxylate and cyclohexyl-
15 carboxylate esters are relatively ineffective even at 16 mg dose, it was found that their oximes at an 8 mg dose were comparable with DMPA, which in this series gave lower results than in the first series. The two oximes also were
surprisingly more effective than closely related ester
20 oximes such as levo-norgestrel cyclobutylcarboxylate 3-oxime and levo-norgestrel-(4'-methyl)cyclohexylcarboxylate 3-oxime.

Again, it was noted that the cyclopentyl and cyclohexyl carboxylate 3-oximes gave better results when formulated

as an aqueous microcrystalline suspension of particle size 3 to 10 μ expressed as the 50% cumulative oversize in the Coulter distribution curve.

It has been observed that progestogens themselves
5 give rise to some endometrial bleeding between injections, but the tests on the preferred oximes indicate that they have a reduced tendency to cause such bleeding and so are more attractive.

In the accompanying drawings, Fig.III formulation 1
10 was based on depot-medoxy-progesterone-acetate and the following formulations were based on oximes of

2. levo-norgestrel
3. levo-norgestrel butanoate
4. levo-norgestrel isobutanoate
- 15 5. levo-norgestrel isovalerate
6. levo-norgestrel cyclopropylcarboxylate
7. levo-norgestrel cyclobutylcarboxylate
8. levo-norgestrel (3'-methyl) cyclohexylcarboxylate
9. levo-norgestrel (3'-ethyl) cyclohexylcarboxylate
- 20 10. levo-norgestrel cyclopentylcarboxylate
11. levo-norgestrel cyclohexylcarboxylate
12. levo-norgestrel (4'-methyl) cyclohexylcarboxylate
13. levo-norgestrel acetate

Table I Effect of levonorgestrel esters on the duration of estrus suppression in mature cycling rats.

E S T E R		Dose per rat mg	Vehicle	Duration of suppression in days mean \pm SD
Compound	Structure			
levonorgestrel		2	AQ	19.5 \pm 1.6
		4	AQ	43.7 \pm 2.7
		8	AQ	52.9 \pm 3.9
formate		16	AQ	29.7 \pm 2.2
acetate		2	AQ	13.1 \pm 0.9
		4	AQ	16.1 \pm 1.8
		8	AQ	27.9 \pm 1.5
propanoate		2	AQ	17.3 \pm 1.1
		4	AQ	26.5 \pm 1.6
		8	AQ	45.6 \pm 2.5
2-methylpropanoate		16	AQ	5.7 \pm 2.7
butanoate		2	AQ	34.4 \pm 2.8
		4	AQ	65.1 \pm 5.9
		8	AQ	91
(S)-2-methylbutanoate		16	AQ	3.5 \pm 1.2
2-ethylbutanoate		16	AQ	3.1 \pm 0.7
3-methylbutanoate		16	AQ	40.3 \pm 2.5
		16	AQ	42.7 \pm 1.8
		16	AQ	53.4 \pm 3.1
3,3-dimethylbutanoate		16	AQ	3.7 \pm 1.3
pentanoate		2	AQ	13.6 \pm 1.5
		4	AQ	27.7 \pm 3.0
		8	AQ	39.3 \pm 3.3
		16	AQ	74.3 \pm 15.6
5-methylpentanoate		16	AQ	50.3 \pm 4.7

Table I (Cont'd.)


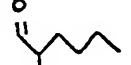
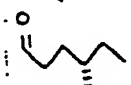



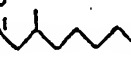


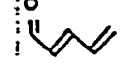


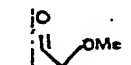
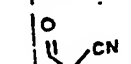

E S T E R		Dose per rat mg	Vehicle	Duration of suppression in days mean \pm SD
Compound	Structure			
hexanoate		16	AQ	22.6 \pm 1.0
2-ethylhexanoate		16	EO	2.6 \pm 0.8
		16	AQ	1.2 \pm 0.4
(S)-4-methylhexanoate		16	AQ	46.6 \pm 3.3
heptanoate		16	EO	22.7 \pm 3.7
		16	EO	26.2 \pm 3.7
		16	EO	31.2 \pm 2.9
		16	AQ	34.0 \pm 2.8
octanoate		16	AQ	25.6 \pm 1.8
nonanoate		16	EO	7.5 \pm 2.8
3-methylnonanoate		16	EO	1.9 \pm 0.4
decanoate		16	EO	15.5 \pm 3.5
E-2-methylpent-2-enoate		16	AQ	2.5 \pm 0.6
E-penta-2,4-dienoate		16	AQ	34.8 \pm 0.4
E,E-2-methylhexa-2,4-dienoate		16	AQ	9.2 \pm 1.5
E-5-phenylpent-2-en-4-ynoate		16	EO	5.7 \pm 0.6
		16	AQ	1.6 \pm 0.4
methoxyacetate		16	AQ	29.5 \pm 1.8
cyanoacetate		16	AQ	85.0 \pm 3.0
cyclopropylcarboxylate		2	AQ	44.9 \pm 2.2
		2	AQ	29.0 \pm 1.7
		4	AQ	68.3 \pm 3.5
		4	AQ	42.8 \pm 2.3
		8	AQ	74.0
		8	AQ	74.1 \pm 2.3

Table I (Cont'd.)















E S T E R		Dose per rat mg	Vehicle	Duration of suppression in days mean \pm SD
Compound	Structure			
cyclobutylcarboxylate (*average of 6 assays)		2 4 6	AQ AQ AQ	31.9* 55.7* 93.8*
2-methylcyclobutyl- carboxylate		16	AQ	55.2 \pm 3.1
2-ethylcyclobutyl- carboxylate		16	AQ	33.6 \pm 6.6
2-hexylcyclobutyl- carboxylate		16	AQ	46.1 \pm 4.4
3-cyclobutyl- propanoate		16	AQ	39.5 \pm 2.1
5-cyclobutyl- pentanoate		16	EO	14.4 \pm 6.8
7-cyclobutyl- heptanoate		16	EO	3.3 \pm 1.1
cyclopentyl- carboxylate		16	AQ	3.9 \pm 1.2
cyclopent-1- enylacetate		16	AQ	16.3 \pm 2.4
cyclohexylcarboxylate		16	AQ	6.5 \pm 2.6
trans-4-methylcyclo- hexylcarboxylate		16	AQ	19.1 \pm 2.2
trans-4-hexylcyclo- hexylcarboxylate		16	AQ	1.9 \pm 0.3
cyclohexylacetate		16	AQ	1.7 \pm 0.3
cyclohex-1-enyl- acetate		16	AQ	2.9 \pm 0.3

Table I (Cont'd.)


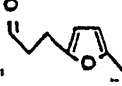
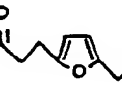
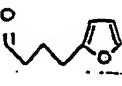
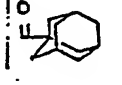
E S T E R		Dose per rat mg	Vehicle	Duration of suppression in days mean \pm SD
Compound	Structure			
5'-methyl-2'-furyl- acetate		16	EO	41.6 \pm 5.2
		16	AQ	47.6 \pm 3.4
3-(5'-methyl-2'- furyl)propanoate		16	AQ	47.0 \pm 3.4
3-(5'-ethyl-2'- furyl)propanoate		16	EO	29.2 \pm 3.2
		16	AQ	21.1 \pm 3.5
4-(5'-methyl-2'- furyl)butanoate		16	AQ	2.8 \pm 0.6
adamantylcarbox- ylate		16	AQ	2.4 \pm 0.8

Table II Effect of Formulation and Vehicle on Duration of Action of Levonorgestrel Esters

Ester	Formulation	Vehicle	Dose mg/ Rat	Response Days Mean \pm SD
cyclobutyl- carboxylate (121)	solution	EO + BB	2	14.7 \pm 2.7
	suspension	EO	4	24.3 \pm 1.9
	suspension	EO	8	49.9 \pm 6.7
	suspension	AQ	2	26.6 \pm 1.6
	suspension	AQ	4	66.9 \pm 2.9
	suspension	AQ	8	124.3 \pm 9.2
butanoate (99)	solution	EO + BB	2	19.1 \pm 2.2
	suspension	AQ	2	34.4 \pm 2.8
pentanoate (104)	solution	EO + BB	2	1.3 \pm 0.3
	suspension	AQ	2	13.6 \pm 1.5
heptanoate (109)	solution	EO	16	31.2 \pm 2.9
	suspension	AQ	16	34.0 \pm 2.8
5'-methyl- 2'-furyl acetate (135)	solution	EO	16	41.6 \pm 5.2
	suspension	AQ	16	47.6 \pm 3.4
5'-ethyl- 2'-furyl propanoate (136)	solution	EO	16	29.2 \pm 3.2
	suspension	AQ	16	21.9 \pm 3.5

CLAIMS:

1. An ester of levo-norgestrel and an aliphatic acid characterized in that the ester is:

levo-norgestrel butanoate,

5 levo-norgestrel cyclopropylcarboxylate,

levo-norgestrel cyclobutylcarboxylate,

levo-norgestrel cyclopentylcarboxylate 3-oxime, or

levo-norgestrel cyclohexylcarboxylate 3-oxime.

2. An ester of levo-norgestrel and an aliphatic acid characterized in that the ester is levo-norgestrel butanoate.

3. An ester of levo-norgestrel and an aliphatic acid characterized in that the ester is levo-norgestrel cyclopropylcarboxylate.

15 4. An ester of levo-norgestrel and an aliphatic acid characterized in that the ester is levo-norgestrel cyclopentylcarboxylate 3-oxime.

5. An ester of levo-norgestrel and an aliphatic acid characterized in that the ester is levo-norgestrel
20 cyclohexylcarboxylate 3-oxime.

6. An injectable contraceptive composition which is a suspension of a levo-norgestrel ester in a pharmaceutically acceptable aqueous medium characterized in that the ester is one claimed in any preceding claim.

5 7. A composition as claimed in Claim 6 characterized in that the ester is suspended in the form of microcrystals of particle size in the range 3 to 10 μ expressed as the 50% cumulative oversize in the Coulter distribution curve.

8. A method of contraception wherein there is injected 10 into a human female a dose of a composition which is an aqueous suspension of a levo-norgestrel ester characterized in that the composition is as claimed in Claim 6 or 7 and the dose contains from 1 to 50 mgms of the ester.

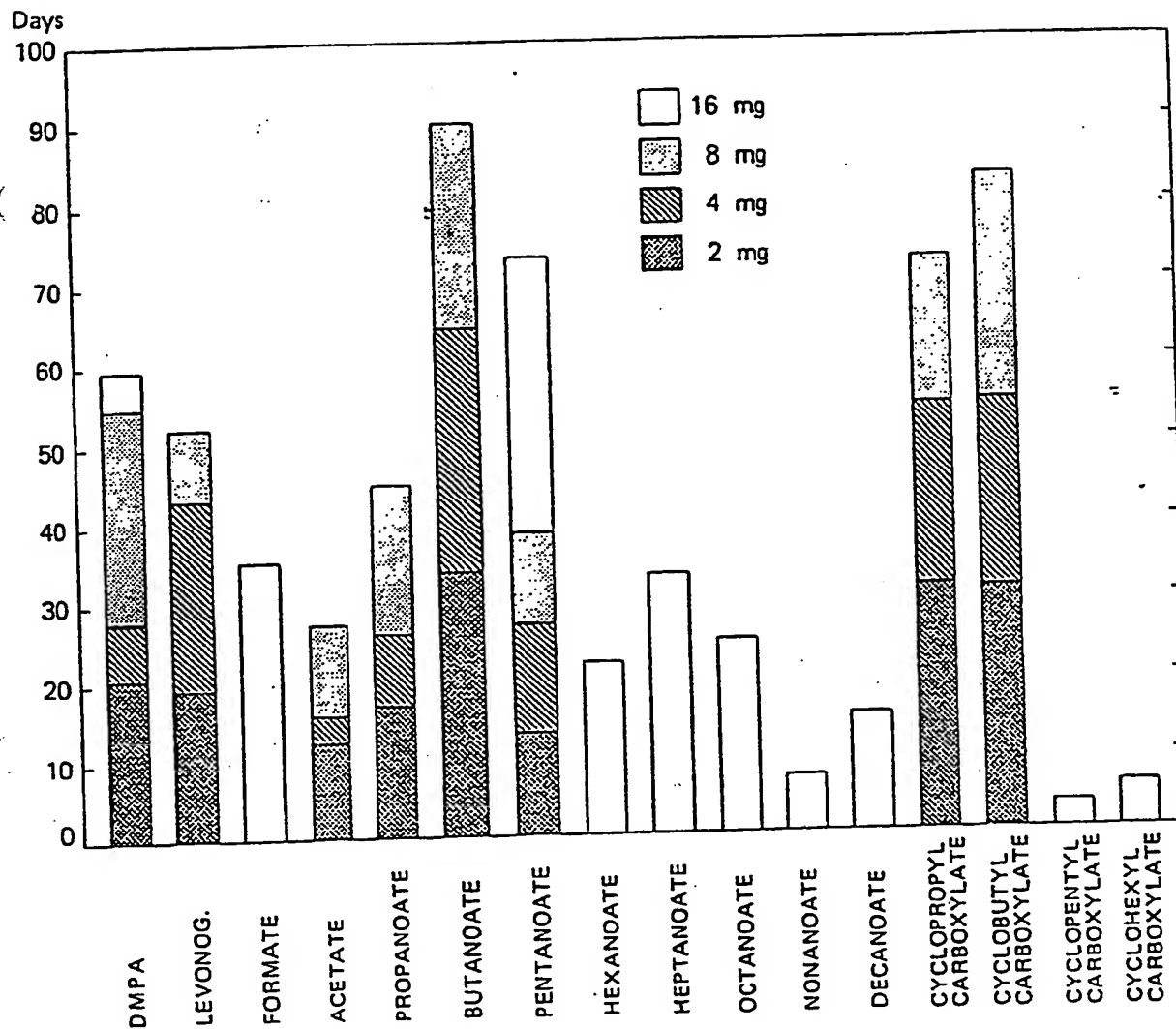
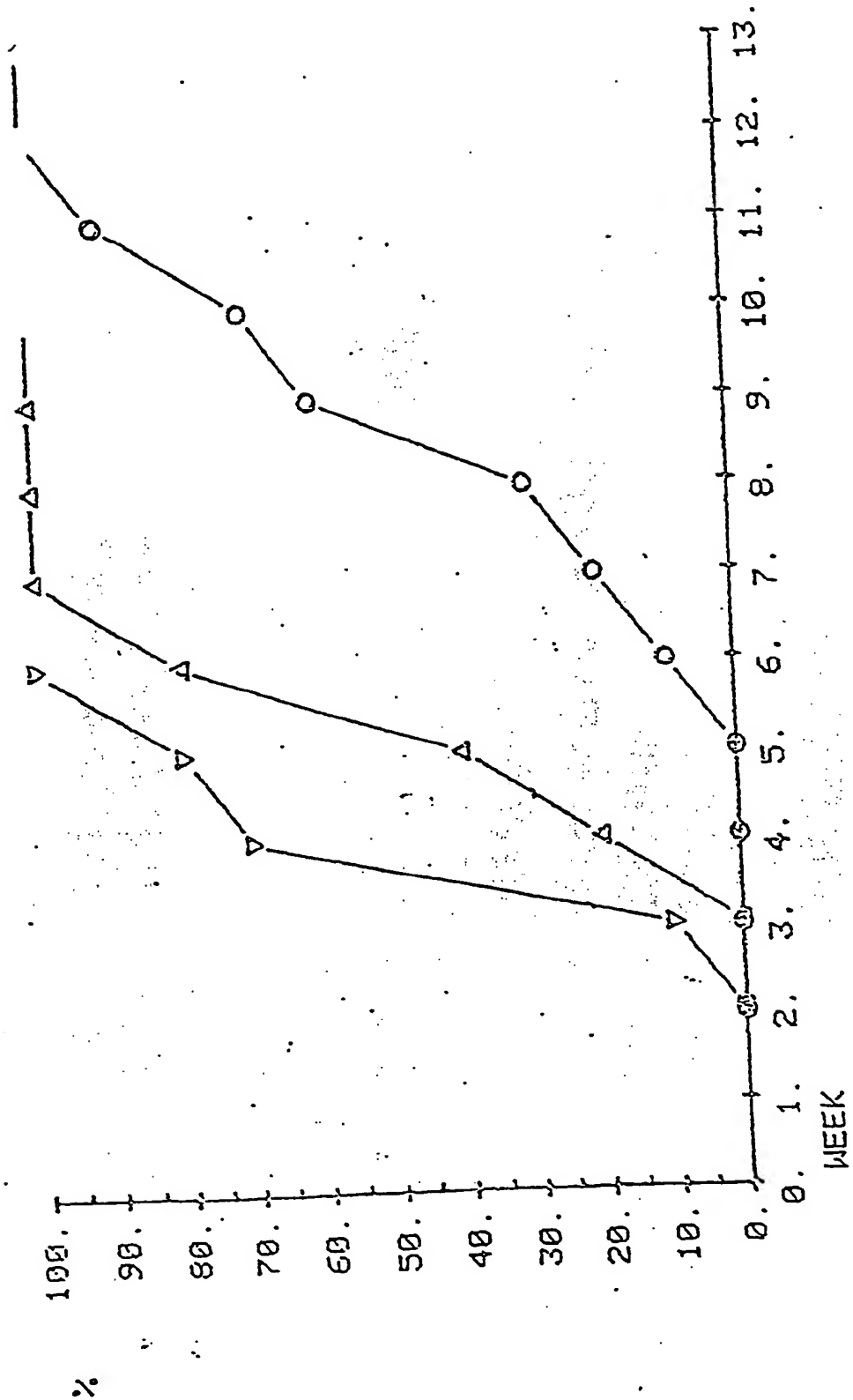


Figure 1. Duration of total estrus suppression following a single subcutaneous injection of levonorgestrel or its esters to rats.

FIG. II

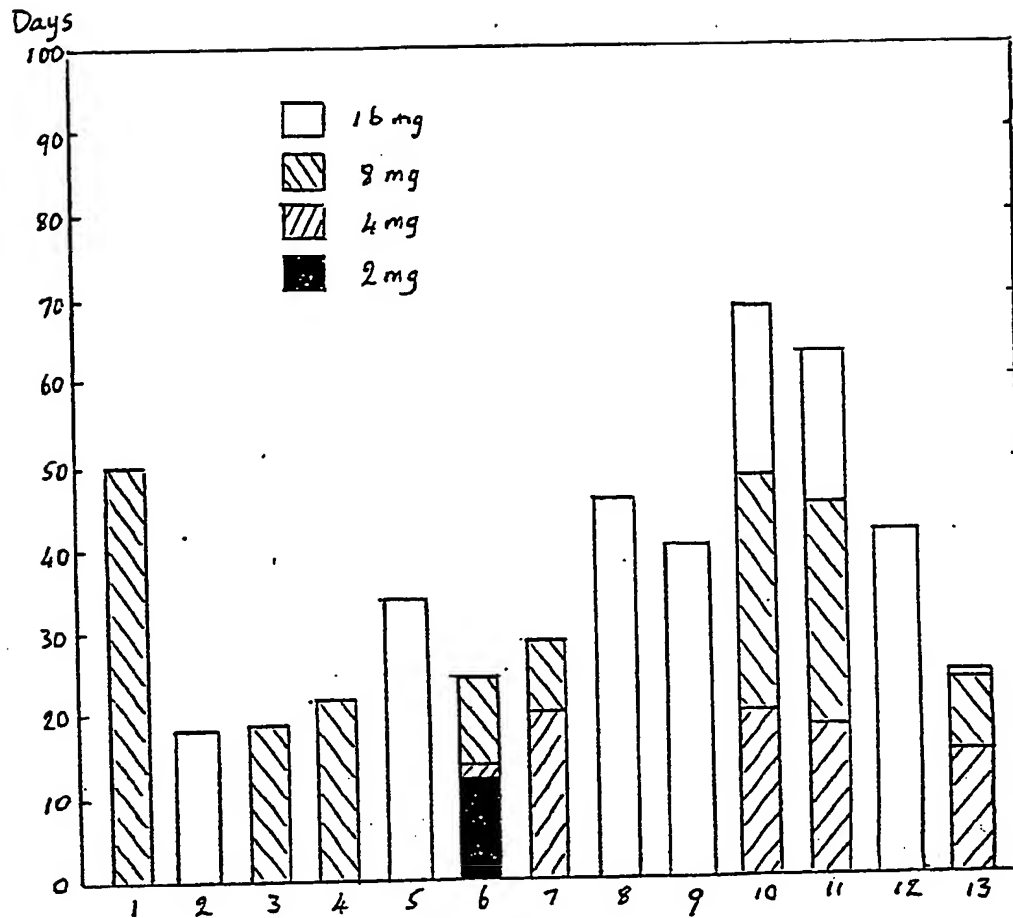


Figure III. Duration of total estrus suppression following a single subcutaneous injection of oximes to rats.

EUROPEAN PATENT APPLICATION

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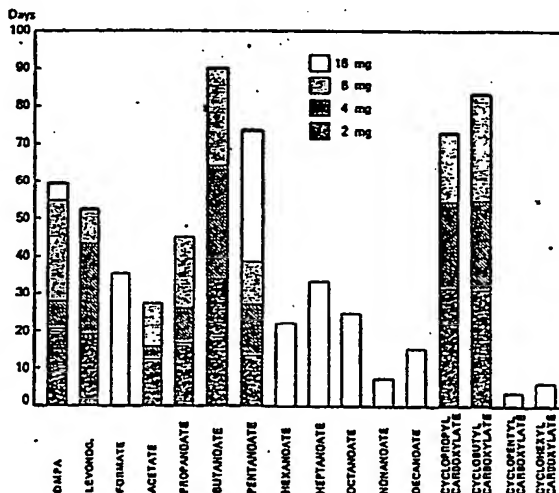
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Contraceptive compositions based on esters of levo-norgestrel.

A small group of esters of levo-norgestrel have been found to be unexpectedly effective as long term contraceptive agents. The esters are:

levo-norgestrel butanoate,
levo-norgestrel cyclopropylcarboxylate,
levo-norgestrel cyclobutylcarboxylate,
levo-norgestrel cyclopentylcarboxylate 3-oxime, or
levo-norgestrel cyclohexylcarboxylate 3-oxime.

The esters may be formulated in a pharmaceutically acceptable aqueous medium, preferably in the form of a microcrystalline suspension of particle size in the range 3 to 10 μ expressed as the 50% cumulative oversize in the Coulter distribution curve. A suitable human dosage contains from 1 to 50 mgms of the ester.





European Patent
Office

EUROPEAN SEARCH REPORT

0129947
Application Number
EP 84 30 0611

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
X	STEROIDS, vol. 41, no. 3, March 1983, pages 349-359, Holden-Day, San Francisco (US), A. SHAFIEE et al.: "Long-acting contraceptive agents: aliphatic and alicyclic carboxylic esters of levonorgestrel". * Pages 351-355 *	1-3, 6-8	C 07 J 1/00 C 07 J 41/00 A 61 K 31/565
X	Idem, pages 419-439, G. BIALY et al.: "Long-acting contraceptive agents: structure activity relationships in a series of norethisterone and levonorgestrel esters". * Pages 419-427 and 435-439 *	1-3, 6-8	
X	BULLETIN DES SOCIETES CHIMIQUES BELGES, vol. 92, no. 3, March 1983, Brussels (BE), pages 275-287, PIERRE CRABBE et al.: "Long-acting contraceptive agents: X-ray study of levonorgestrel esters".	1-3, 6-8	TECHNICAL FIELDS SEARCHED (Int. Cl. 3) A 61 K C 07 J
X	CHEMICAL ABSTRACTS, vol.97, no.21, 22 November 1982, page 860, abstract 182724x (COLUMBUS OHIO, US); R. VLAKHOV et al.: "Synthesis of some esters of norethisterone and d-levonorgestrel as possible fertility regulators". -/-	1,3,	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 05-12-1984	Examiner HENRY J.C.
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DOCUMENTS CONSIDERED TO BE RELEVANT					
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)		
A	& Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. (Proc.), 1st 1981 2, 425-436 * Abstract * ----- FR-A-2 318 645 (ORTHO) * Claims 1, 15 * -----	4-8			
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)		
The present search report has been drawn up for all claims					
Place of search		Date of completion of the search	Examiner		
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